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Unrelated Donor Umbilical Cord Blood Transplantation in Pediatric Myelodysplastic Syndrome: A Single-Center Experience

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Myelodysplastic syndromes (MDS) respond poorly to chemotherapy. Between 1995 and 2006, 23 pediatric patients with MDS were transplanted with unrelated donor umbilical cord blood (UUCB) at our center. The median age was 11.1 years (range: 1.1-19.7), median weight was 38.6 kg (range: 9.6-62.6), 61% of patients were male, and median time from diagnosis to transplant was 6.6 months (range: 2.0-61.4). Patients were followed for a median of 5.3 years (range: 1.6-12.4 years) posttransplant. MDS stage was refractory anemia (RA) in 12, refractory anemia with excess blasts (RAEB) in 8, and refractory anemia with excess blasts in transformation (RAEB-T) in 3 patients; 18 (78%) patients had primary MDS. Monosomy 7 was present in 17(74%) patients. Patients with acute myelogenous leukemia (AML) were excluded. Preparative regimen was total body irradiation (TBI) based in 18 (78%) patients. Graft-versus-host-disease (GVHD) prophylaxis was cyclosporine (CsA)/steroids (19 patients) or CsA/mycophenolate mofetil (MMF; 4 patients). Grafts were HLA matched at Class I (A and B) at low resolution and Class II (DRB1) at the allelic level, resulting in 16 (70%) 4/6 and 7 (30%) 5/6 matched transplants. The grafts contained a median of 4.0×10^7 (range: 1.7-12.6) total nucleated cells (TNC)/kg precryopreservation; 3.6×10^7 (range: 1.0-12.0) TNC/kg and 1.7×10^5 (range: 0.2-28.5) $CD34^+$ cells/kg were infused. Cumulative incidence of neutrophil engraftment (absolute neutrophil count [ANC] $>500/\mu L$) at day 42 and day 100 was 73.9% (95% confidence interval [CI] 55.1%-92.7%) and 91.3% (95% CI 71.3%-100.0%) respectively, and that of platelet engraftment (50 K) at 180 days was 69.6% (95% CI 49.8%-89.4%). Three patients had graft failure whereas 3 patients (13%) engrafted slowly (after day 42). Three patients developed acute GVHD (aGVHD) grades II-IV with a cumulative incidence at 100 days of 13% (95% CI 0.0%-27.1.0%). Four patients relapsed with a cumulative incidence of relapse at 3 years of 13.0% (95% CI 0.0%-27.1%). Cumulative incidence of nonrelapse mortality (NRM) at 1 year was 27% (95% CI 8.0%-46.0%). Ten patients died: 3 graft failure, 4 relapse, 2 infections (1 adenovirus, 1 toxoplasmosis), and 1 Epstein-Barr virus (EBV) lymphoproliferative disorder. Probabilities of event-free survival (EFS) at 1 and 3 years were 69.6% (95% CI 46.6%-84.2%) and 60.9% (95% CI 38.3%-77.4%), respectively. Factors associated with better EFS were age $\leq$11 years ($P = .05$) and weight $\leq$38 kg ($P = .03$). These results, especially in younger patients with monosomy 7 positive MDS, are equivalent to published matched allogeneic bone marrow data. UUCB should be actively considered for pediatric MDS patients lacking matched related or unrelated adult donors.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are heterogeneous disorders of hematopoietic stem cells, characterized by bone marrow (BM) dysplasia, ineffective hematopoiesis leading to progressive cytopenias, and a variable tendency to evolve into acute myelogenous leukemia (AML). MDS is more commonly seen in adults where the incidence ranges from 3.5 to 12.6 cases/100,000 population/year [1]. The incidence in adults increases with age, and has been reported to be as high as 89 cases/100,000 beyond 80 years of age [2]. Cytogenetic abnormalities, including monosomy 5 and/or 7,

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are seen in 40% to 70% of patients with primary MDS and in 95% of patients with secondary MDS [3,4].

Childhood MDS differs from adult MDS in several ways. MDS is more rare in children with an overall incidence of approximately 3 to 4 million [5,6]. The biology of MDS also differs in children. Not only are cytogenetic abnormalities far more common in children, but the type of abnormalities tend to differ, with monosomy 7 being more common in childhood MDS and 5q- more common in adults. The International Prognostic Scoring System (IPSS), which utilizes biologic parameters such as blast percentage, complexity of cytogenetics, and degree of cytopenias, and is useful in risk stratification in adult MDS patients, appears to be of limited value in guiding pediatric MDS therapy, again underscoring the biologic differences [7]. Treatment approaches are quite different in childhood MDS. The intent of treatment in children with MDS is cure, as opposed to adults, where palliation is often the most feasible approach. Even though spontaneous remissions of MDS with monosomy 7 have been reported, these are rare and do not preclude initiation of therapy with a curative intent [8]. Intensive chemotherapy, similar to treatment in patients with newly diagnosed AML, can induce remissions in 15% to 60% of patients, but these remissions are not durable, resulting in high relapse rates and overall survival (OS) of <30% [9-11]. Autologous stem cell transplant (SCT) after high-dose chemotherapy is also associated with a high relapse rate. Allogeneic SCT, using bone marrow (BM) or other hematopoietic stem cell (HSC) sources, offers the best chance for cure with long-term survival in approximately half to two-thirds of patients [12-15].

More than half of MDS patients in need of SCT are unable to find a suitably HLA matched related or unrelated living donor [16]. For such patients, partially mismatched unrelated donor umbilical cord blood (UUCB), which has been established as an alternative source of stem cells for allogeneic transplantation for a variety of malignant and nonmalignant disorders, may be a potential source of graft. There is very limited data on outcomes of UUCB transplantation in pediatric patients with MDS. We now describe outcomes of this therapy in 23 pediatric patients with MDS with or without monosomy 7 treated at a single institution.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of all consecutive patients with MDS who underwent hematopoietic stem cell transplantation (HSCT) at the Pediatric Blood and Marrow Transplantation Program of Duke University Medical Center between 1995 and August 2006. Data were analyzed as of April 25, 2008. Subsets of these patients were included in an abstract at the 2008 American Society of Hematology annual meeting [17] and in the COBLT malignancy cohort [18]. Patients were classified according to the modified WHO classification scheme suggested by Hasle et al. [19]. The highest blast percentage during the period from diagnosis of MDS to transplant was used to classify patients by the above-mentioned classification.

Patients who were <20 years of age at the time of transplant were included if they received UUCB transplant after myeloablative (MA) conditioning regimen, had not had a previous transplant, and did not have Fanconi anemia (FA), Down syndrome, or other constitutional BM failure disorders. Juvenile myelomonocytic leukemia (JMML) cases and patients with MDS who evolved to frank AML prior to transplant were excluded.

Informed consent was obtained from the parent or legal guardian of all patients prior to initiating MA conditioning therapy.

Donor Selection

Grafts were matched at HLA Class I (A and B) at low-resolution and HLA Class II (DRB1) at the allelic level. Grafts were obtained from 6 public cord blood banks in the United States (NYBC, Duke, ARC, UCLA, Stemcyte, ITxM).

Preparative Regimen and graft-versus-host disease (GVHD) Prophylaxis

An MA preparative regimen was used in all patients. Eighteen patients were treated with a total body irradiation (TBI)-based regimen (TBI/cyclophosphamide [Cy]/antithymocyte globulin [ATG] in 8 patients, TBI/melphalan [Mel]/ATG in 10 patients) and 5 patients received a busulfan (Bu)-containing, chemotherapy-based regimen (Bu/Mel/ATG in 2 patients, fludarabine [Flu]/Bu/Mel/ATG in 1 patient, Rituximab/Flu/Bu/Mel/ATG in 1 patient, and Bu/Cy/ATG in 1 patient). First-dose Bu pharmacokinetics was obtained in all patients and used to adjust the steady-state concentration (C_{ss}) to 600 to 900 ng/mL over the dosing period. GVHD prophylaxis consisted of cyclosporine (CsA) with methylprednisolone in 19 patients and CsA with mycophenolate mofetil (MMF) in 4 patients.

Supportive Care

All patients were hospitalized in the Pediatric bone marrow transplant (BMT) unit of Duke University Medical Center and nursed in reverse isolation under high-energy particulate air filtration and positive-pressure ventilation. Patients were treated with broad-spectrum antibiotics, starting with the first episode of neutropenic fever and continued until neutropenia resolved. All patients received prophylaxis against *Pneumocystis carinii*, fungal prophylaxis with fluconazole, amphotericin B, or

voriconazole, and antiviral prophylaxis with acyclovir. All patients received intravenous immunoglobulin (IVIG) once a week for the first 100 days and once a month thereafter for the first year posttransplant. Low-dose continuous .v. heparin infusion was employed from the initiation of the preparative regimen through posttransplantation day 28 for prophylaxis against veno-occlusive disease (VOD). All patients were supported as needed with transfusions of leukocyte-depleted, irradiated packed red blood cells, and platelets. Filgrastim (Amgen, Thousand Oaks, CA) was administered i.v. at 10 μg/kg/day from day 0 until engraftment of donor cells and then tapered.

Statistical Methods

Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count (ANC) $>500/\mu$L along with evidence of >90% donor chimerism. Donor chimerism was assessed using HLA, fluorescein in situ hybridization (FISH) or restriction fragment-length polymorphism (RFLP) techniques. Platelet engraftment was defined as the first day of achieving platelet count of 50 K/μL without receiving transfusion in the previous 7 days. Primary graft failure was defined as lack of donor cell chimerism by day 42 posttransplant along with failure to achieve ANC $>500/\mu$L or if the patient died after day 14 without evidence of ANC >500 with or without donor cell chimerism. Delayed engraftment was defined as evidence of donor cell chimerism by day 42, but achieving ANC >500/μL after day 42. Relapse was defined as the recurrence of previous cytogenetic marker, and/or morphologic evidence of MDS or AML. Acute and chronic GVHD (aGVHD, cGVHD) were scored by conventional criteria [20,21]. The probabilities of neutrophil and platelet engraftment, aGVHD and cGVHD, and relapse were estimated for all patients transplanted surviving past 14 days using the cumulative-incidence-function method [22].

OS was calculated from the date of transplant to the date of death or date of last follow-up using the Kaplan-Meier estimator [23], and the differences were compared using log-rank statistics [24]. Cox proportional hazards regression was used to create exploratory prognostic models with multiple variables [25]. Multivariate models were then constructed using backward stepwise selection. Variables considered for the model were those with a P value of .20 or less in the univariate analysis. Variables with a value of $P <$ .05 were considered statistically significant and included in the final model. All variables met the proportional hazards assumption. Results were expressed as hazard ratios, which compare the relative rate of event occurrence between covariate categories. Baseline variables considered include age at transplant, recipient sex, donor sex, sex mismatch, type of MDS (primary or secondary to therapy), disease stage, cell dose—total nucleated cells (TNC) cryopreserved and reinfused, $CD34^+$ reinfused, HLA match, recipient race, donor race, ABO mismatch recipient weight, time from diagnosis to transplant, karyotype, TBI, and Mel conditioning regimen, and whether the recipient received chemotherapy prior to transplant. All P values were 2 sided. The same analyses were carried out on event-free survival (EFS), which was calculated from the date of transplant to the date of event—death, relapse, or graft failure; and on time to engraftment, which included delayed engraftment. Analyses were completed using the SAS system version 8.2, and R version 2.6.0. (SAS Institute, Cary, NC).

Table 1. Patient and Transplant Characteristics (N = 23)

Variable	Median	Range
Age, years	11.1	1.1-19.7
Weight, kg	38.6	9.6-62.6
Follow-up, years	5.3	1.6-12.4
Time from diagnosis to transplant, months	6.6	2-61.4
Cellular characteristics		
TNC pre-cryo (10^7/kg)	4.0	1.7-12.6
TNC infused (10^7/kg)	3.6	1.0-12.0
$CD34^+$ (10^5/kg)	1.7	0.2-28.5
	No. of patients	**%**
Sex, male	14	61%
Ethnic minorities	5	22%
CMV seropositive recipient	13	57%
Type of MDS		
Primary MDS	18	78%
Therapy related-MDS	5	22%
Disease stage		
RA	12	52%
RAEB	8	35%
RAEB-t	3	13%
Cytogenetics		
Mono 7	17	74%
Other	2	9%
Normal	4	17%
Match characteristics		
HLA mismatch		
0	0	0
1	7	30%
2	16	70%
ABO matched	17	74%
Sex matched	11	48%
Ethnicity matched	15	65%
Conditioning		
TBI based	18	78%
Busulfan based	5	22%
GVHD prophylaxis		
CsA/methylprednisolone	19	83%
CsA/MMF	4	17%

CMV indicates cytomegalovirus; MDS, myleodysplastic syndromes; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; TBI, total body irradiation; GVHD, graft-versus-host disease; CsA, cyclosporine; MMF, myeophenolate mofetil.

RESULTS

Patients

Twenty-three patients were enrolled on this study. All patients were transplanted with unrelated UCB units

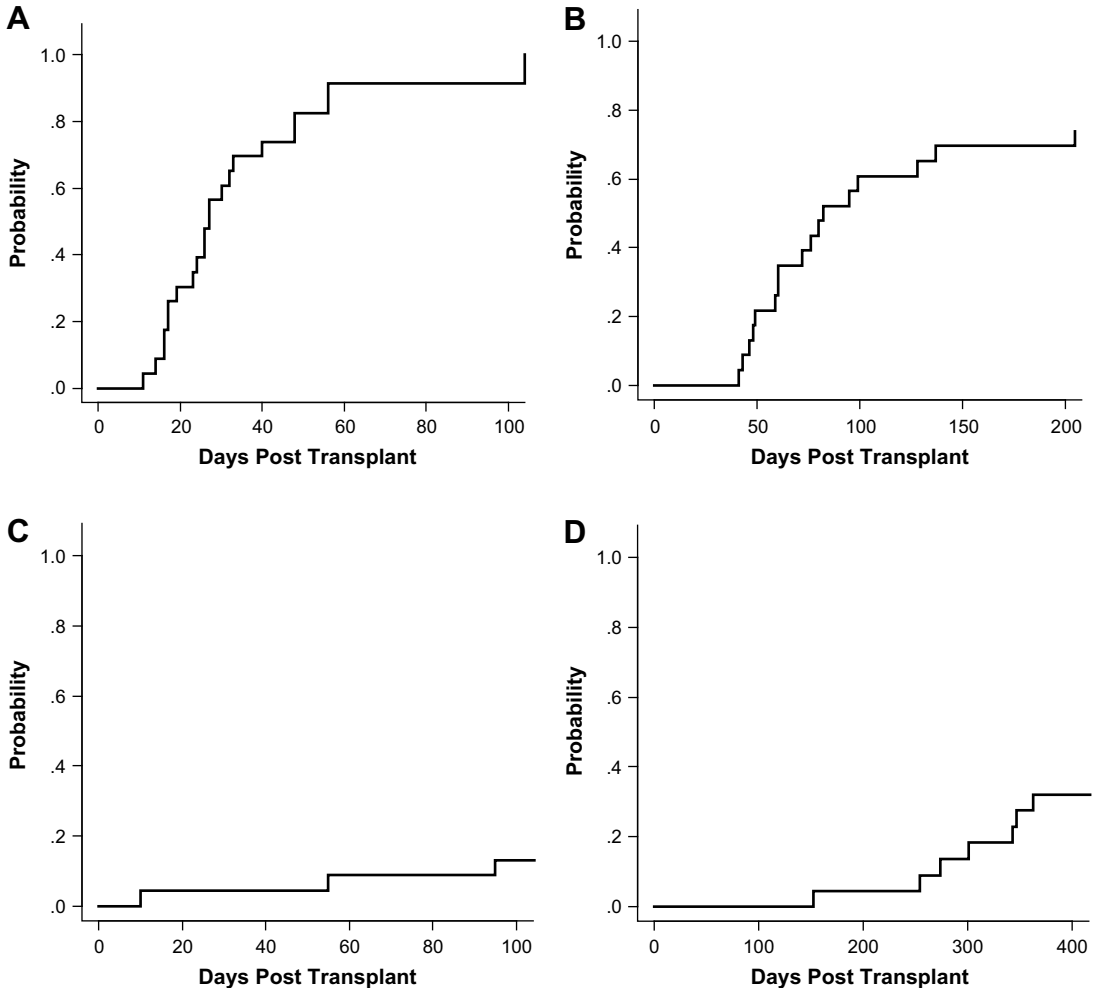

Figure 1. (A) Cumulative incidence of neutrophil engraftment. (B) Cumulative incidence of platelet engraftment 50K. (C) Cumulative incidence of aGVHD II-IV. (D) Cumulative incidence of cGVHD.

after MA conditioning. Detailed patient characteristics are shown in Table 1. Briefly, 14 patients (61%) were male, and 5 patients (22%) belonged to racial minorities. Median weight at the time of transplant was 38.6 kg (range: 9.6-62.6 kg). Median ages at diagnosis of MDS and transplant were 9.6 years (range: 0.6-19.1 years) and 11.1 years (range: 1.1-19.7 years), respectively. Median time from the diagnosis of MDS to transplant was 6.6 months. Eighteen (78%) patients had primary MDS, whereas the remaining 5 (22%) had therapy-related MDS. Disease stage was refractory anemia (RA) in 12 (52%) patients, refractory anemia with excess blasts in transformation (RAEB) in 8 (35%) patients, and refractory anemia with excess blasts in transformation-transformed RAEB-T in 3 (13%) patients. Ten patients received therapy within 12 months of transplant, which consisted of cytotoxic chemotherapy in 5 patients, immunosuppressive therapy (with CsA containing regimens) in 4 patients, and amifostine/erythropoietin in 1 patient. Thirteen (57%) patients were cytomegalovirus (CMV) seropositive prior to transplant.

Table 2. Causes of Death

Causes of Death	Primary	Secondary
Relapse	4	
Graft failure	3	
Infection	2	
EBV LPD	1	1
MSOF		4

EBV LPD indicates Epstein Barr Virus associated lymphoproliferative disease; MSOF, multisystem organ failure.

Cytogenetics

Karyotypes in abnormal cells were normal in 4 (17%) patients, showed monosomy 7 in 17 (74%) patients, trisomy 8 in 1 patient, and t(2,3) with rearrangement in chromosome 5 in 1 patient. Four patients with monosomy 7 had additional complex cytogenetic abnormalities.

Donors

All patients received single umbilical cord blood (UCB) grafts, except 1 patient who received double UCB grafts. All 23 patients received partially mismatched graft: 7 (30%) from a 5/6 and 16 (69%) from

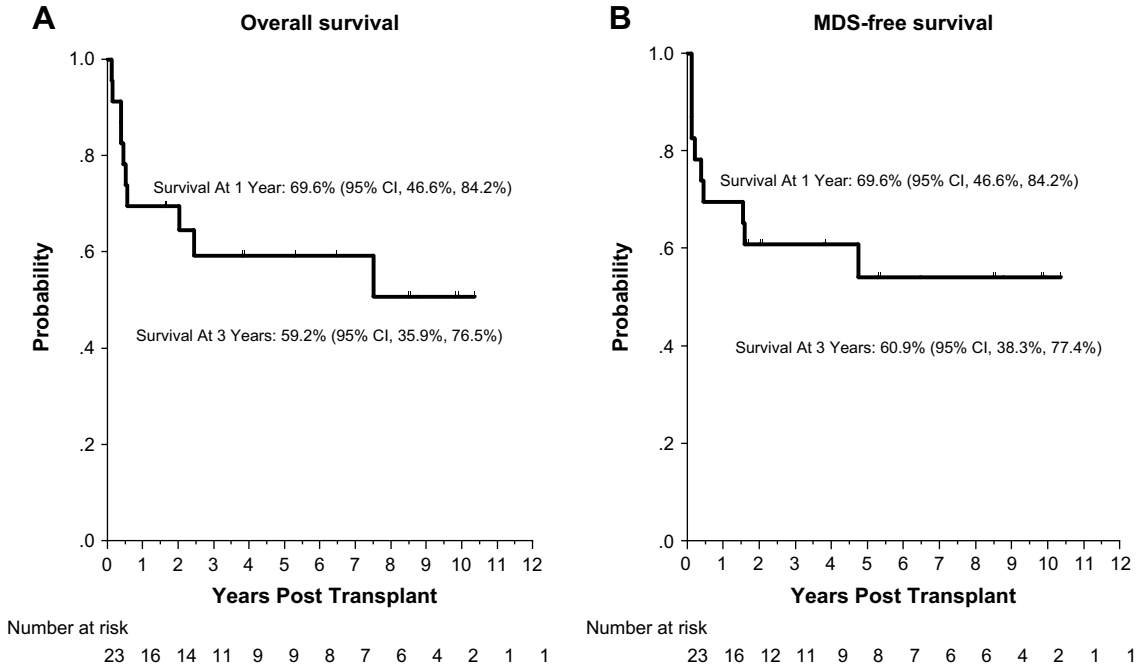

Figure 2. (A) Kaplan-Meier estimates of OS. (B) Kaplan-Meier estimates of MDS-free survival.

a 4/6 HLA matched unit. The grafts delivered a median of 4.0×10^7 (range: 1.7-12.6) nucleated cells/kg based on precryopreservation count. The median reinfused TNC dose was 3.6×10^7cells/kg (range: 1.0-12.0) and contained a median CD 34^+ cell dose of 1.7×10^5/kg (range: 0.2-28.5). The grafts were ABO matched in 17 (74%) patients, sex matched in 11 (48%) patients, ethnicity matched in 15 (65%) patients.

Engraftment

By day 42, 17 of the 23 engrafted with donor cells. Three additional patients engrafted after day 42 at days 48, 56, and 104. Of the 20 engrafting patients, the median time to neutrophil engraftment (ANC $>500/\mu$L) was 26 days (range: 11-104 days). Cumulative incidences of neutrophil engraftment at day 42 and day 100 were 73.9% (95% confidence interval [CI] 55.1%-92.7%) and 91.3% (95% CI 73.1%-100.0%), respectively (Figure 1A). Three patients experienced primary graft failure and subsequently died of transplantation-related complications, despite salvage transplant in 2 of these 3 patients. Seventeen patients achieved platelet engraftment in a median of 72 days (range: 41-205 days). Cumulative incidence of platelet engraftment at day 100 was 60.9% (95% CI 40.1%-81.7%) and at day 180 was 69.6% (95% CI 49.8%-89.4%) (Figure 1B). No significant predictors of engraftment or graft failure were identified from the variable set tested.

GVHD

aGVHD (grades I-IV) was seen in 11 patients. Eight patients experienced grade I aGVHD, 2 had grade II, and 1 experienced grade III. Limited cGVHD was seen in 7 patients, 6 of whom previously had aGVHD. Of these 6 patients, 5 had grade I prior aGVHD, and 1 had grade III prior aGVHD. The median time to the onset of cGVHD was 301 days (range: 152-363). Extensive cGVHD did not occur in any patient. The 1-year cumulative incidence of grade II-IV aGVHD, grade III-IV aGVHD, and cGVHD (all limited) were 13.0% (95% CI 0.0%-27.1%), 4.3% (95% CI 0.0%-12.9%), and 32.1% (95% CI 11.7%-52.5%), respectively (Figure 1C, 1D).

Relapse

Four patients engrafted with donor cells and subsequently experienced a relapse of their MDS in a median of 567.5 days posttransplant (range: 76-1728 days). The cumulative risk of relapse at 3 years was 13% (95% CI 0.0% -27.1%). All relapses occurred in host cells.

Nonrelapse mortality (NRM)

Cumulative risk of NRM at 1 year was 27.0% (95% CI 8.0%-46.0%). Of the 23 patients, 10 died at a median of 173.5 (range: 43-2738) days posttransplant. Causes of death (Table 2) were graft failure, relapse, infection, Epstein-Barr virus (EBV) lymphoproliferative disease, and multisystem organ failure (MSOF).

OS and EFS

OS for all patients at 1 year and 3 years were 69.6% (95% CI 46.6%-84.2%) and 59.2% (95% CI 35.9-76.5), respectively (Figure 2A). EFS was 69.6% (95% CI 46.6%-84.2%) at 1 year and 60.9% (95% CI

Table 3. Univariate and Multivariate Analysis: Impact of Age and Weight on Event-Free Survival (EFS)

Event-Free Survival	Event-Free Survival Probability	Univariate Analysis			Final Multivariate Model (Includes Only Significant Variables)			
Variable	At 3 Years (95% CI)	Hazard Ratio	(95% CI)	*P*-Value	Hazard Ratio	(95% CI)	*P*-Value	Favorable Factors
All patients	60.9% (38.3%-77.4%)	—	—	—				
Age								
≤11 Years	81.8% (44.7%-95.1%)	1.00						
>11 Years	41.7% (15.2%-66.5%)	4.74	(0.99-22.51)	.05				
Recipient Weight (kg)								Weight ≤38 kg
≤38	90.9% (50.8%-98.7%)	1.00			1.00			
>38	33.0% (10.3%-58.8%)	5.61	(1.16-27.11)	.03	5.61	(1.16-27.11)	.03	

CI indicates confidence interval.

38.3%-77.4%) at 3 years (Figure 2B). There was no difference in outcomes between patients with primary or secondary MDS. Monosomy 7 did not influence the outcome. In univariate analysis, age ($P = .04$) and weight ($P = .02$) were statistically associated with OS. Similarly, age ($P = .05$) and weight ($P = .03$) were the only variables that demonstrated a significant influence on EFS survival. Variables considered in an exploratory multivariate analysis were age, weight, type of MDS (primary or secondary), cell dose $\times 10^7$/kg cryopreserved, cell dose $\times 10^7$/kg reinfused. Interactions were also investigated; however, none were found to be significant when the main effects remained in the model. In multivariate analyses only weight remained significant for both OS and EFS (Table 3).

DISCUSSION

Outcomes of pediatric patients with MDS treated with conventional chemotherapy therapy are poor [9,10]. Allogeneic HSCT currently offers the best chance of cure and long-term survival [1,10]. We report outcomes of pediatric patients with MDS treated with UUCB transplant at a single institution. UCB was used as the source of graft in these patients because of unavailability of a suitably matched living related or unrelated BM donor. We excluded patients with JMML and MDS secondary to constitutional disorders such as FA, Kostmann's, etc., because of growing evidence that these disorders are biologically distinct [11,19]. Twenty-three pediatric patients with MDS received UUCB grafts, all of which were mismatched at either 1 or 2 HLA loci. All patients received MA preparative regimen that was predominantly TBI based. EFS was 61% at 3 years, with a median follow-up of 5.3 years. Primary graft failure and relapse were the major causes of treatment failure and death. Recipient weight (≤38 kg) was associated with a favorable outcome in multivariate analysis. Factors such as pretransplant therapy, TBI containing preparative regimens, graft cell dose, HLA matching, ABO mismatching, recipient pretransplant CMV serostatus did not influence OS or disease-free survival (DFS). Althought the impact of weight is consistent with the cord blood experience in other diseases, the lack of impact from the remaining factors may well be the result of the small sample size [26]. Patients in the present study received grafts with a relatively high cell dose (median precryopreservation cell dose of 4×10^7 TNC/kg), which combined with small sample size may have masked the effect of cell dose. No obvious risk factors were found to be associated with the poor outcome in older patients (>11 years) noted only in univariate analysis.

Data from several single institution and multicenter registry studies, reflecting mostly outcomes of adult MDS patients undergoing allogeneic BM transplantation, indicate approximate rates for EFS of 30% to 40%, relapse rate of 20%, and NRM of 40% to 45% [1]. There is relatively limited data on allogeneic transplantation in the pediatric population with MDS and involves BN as the predominant stem cell source (summarized in Table 4). In pediatric studies, the overall rates of EFS has ranged between 15% and 69% with relapse rates of 14% and 26%. Treatment-related mortality (TRM) was high, as observed in the adult studies. Our results compare favorably to these reported studies. The cumulative incidence of engraftment of 91% and median time to engraftment of 26 days are comparable to previously reported unrelated cord blood transplantation registry data from New York Blood Center [27] and slightly better than that reported from European registries [26]. Interestingly, 3 patients engrafted after day 42, one of the patients engrafting after day 100. Although this could be a result of a host of factors, one can speculate that the biology of MDS includes an abnormal BM microenvironment, which contributed to delayed engraftment of the healthy donor cells. In multivariate analysis, engraftment was not affected by any of the variables tested including cell dose, HLA matching, conditioning regimen and pretransplant chemotherapy.

Cumulative incidence of aGVHD II-IV, limited cGVHD, and extensive cGVHD at 1 year in our series was 13%, 32.1%, and 0%, respectively. The incidence of aGVHD was lower compared to that described for BMT patients despite the greater degree of HLA

Table 4. Summary of HSCT Studies in Pediatric MDS

First Author/Center(s)/ Reference	No. of Pts	Diagnoses	Donor Source	Conditioning	EFS	Engraftment	GVHD*	TRM	RR
Locatelli/EWOG-MDS [15]	33	MDS/AML, no JMML	BM(MRD 23)	TBI 11 Bu 22	5 years, 58%	N/A	42%	21%	26%
Locatelli/EBMT.EWOG (Prospective) [17]	89	MDS/AML, no JMML	BM 61PB 26UCB 2 (MRD 35, MUD 54)	Bu/Cy/Mel	4 years, 61%	Median 15 d 87/89 (97%)	MUD 29% MRD 17%	27%	15%
Castro-Malaspina/NMDP [28] †	144	MDS/AML, CMML	BM (All MUD)	Various	2 years, 29%	Median 18 d 84% CI 100d	47%, chronic 27% 2yr	54%	14%
Kardos/Europe [12]	67 (41 transplant)	RA	BM 34 PB 5 UCB 2	TBI 21 Bu 20	6 years, 64%	N/A	N/A	27%	N/A
Yusuf/Seattle [13]	94	All MDS/AML/JMML	BM	Various	3 years, 41%	Median 21 d 92/94 (97.8%)	72%, chronic ext ~20%	28%	30%
Trobaugh-Lotrario/multiple [14]	16	Mono7 AML/MDS	BM 6 PBSC 3 UCB 7 (MRD 7, URD 9)	Various	2 years, 69%	Median 27.5 d	50%	31%	None
Woodard/St. Jude [31]	38	t-AML/MDS	BM (MRD 16, Haplo 3, URD 25)	Various	3 years, 15.4%	N/A	24% III-IV	60%	18%
Strahm/EWOG-MDS[32]	19	RA	BM 14 PBSC 5 (MUD 14, MMUD 5)	RIC: Flu/ Thiotepa/ATG	3 years, 74%	Median 20 d	48%	16%	None
Current study	23	MDS	UCB (All mismatched unrelated)	TBI 18 Bu 5	3 year, 61%	Median 26 d 91% CI 100d	13%	27%	13%

AML indicates actue myelogenous leukemia; ATG, antithymocyte globulin; BM: bone marrow; Bu, busulfan; CI, cumulative incidence; Cy, cyclophosphamide; EFS, event-free survival; Flu, fludarabine; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndromes; Mel, Melphalan; MRD, matched related donor; MUD: matched unrelated donor; N/A, not available; pts, patients; PBSC, peripheral blood stem cell; RA, Refractory anemia; RR, relapse rate; TRM, treatment-related mortality; UCB, umbilical cord blood; URD, unrelated donor.

*GVHD indicates represents grade II-IV acute GVHD, unless qualified.

†One hundred forty-four of 510 patients were <20 years of age, with no significant impact of age noted on multivariate analysis.

mismatch in our patients [13,28] and none of our patients had extensive cGVHD. Yet, the incidence of relapse (13%) in our series was not higher than previous studies. This is consistent with previously reported results using cord blood as a graft source for unrelated donor transplantation [29,30].

TRM or NRM has ranged from 21% to 54% in the larger series involving pediatric patients. In our series, the 1 year TRM was 27%, which is comparable to these studies.

The incidence of monosomy 7 in our series is higher than that in the published data. This could be a result of referral bias, or reflect the heterogeneity of the disease. Presence of monosomy 7 did not have a negative impact on the outcome of patients in our series, similar to the experience of several recent studies, which have suggested that monosomy 7 may not be an independent prognostic factor for patients with pediatric MDS who undergo allogeneic transplant early in the course of their disease [12,14].

Outcomes of patients with therapy-related MDS were comparable to those for de novo MDS in this series. Woodard et al. [31], in a recent report described the outcomes of 38 children with therapy-related MDS and AML, and found the 3-year survival (OS and EFS) to be 15.4% with the TRM of 60%, suggesting that this category of patients have a poor outcome probably because of increased cumulative exposure to previous chemotherapy and/or radiotherapy. The outcome of patients with therapy-related MDS in this series is better, but the number of patients is too small to know if this is a real difference overall. Nevertheless, TRM remains a major challenge in these patients and reduced-intensity conditioning (RIC) regimens need to be studied. In fact, a recent European Working Group (EWOG)-MDS report illustrates the feasibility as well as excellent results of this approach using BM or peripheral blood as graft source in low-risk pediatric patients with RA without clonal abnormalities [32].

In conclusion, our single institution series of unrelated cord blood transplant in pediatric patients with MDS demonstrates that unrelated cord blood transplant is an effective and curative approach in these patients. The presence of monosomy 7 did not adversely affect the outcome after transplantation. Graft failure and relapse were the main causes of treatment failure. Outcomes may be improved in the future by approaches to enhance engraftment of unrelated cord blood grafts, approaches to decrease regimen related toxicity (eg, employing RIC regimens) and/or implementation of newer agents in an attempt to decrease relapse rates (eg, hypomethylating agents) prior to, or as continuation of therapy after transplant in selected patients. The outcomes are best in younger patients, and transplant is thus recommended early in the course of the disease.

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